REMARKS

A check for $510 for the requisite fee for a three-month extension of time accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

Claims 1-15 and 17-64 are pending. Claim 16 is cancelled herein. Claims 1-4, 10, 11, 15, 17 and 35 are amended herein. Claims 1-3 are amended to more distinctly claim the subject matter. Basis for the amendment is found throughout the specification (*e.g.*, see page 3, lines 29-31). Claim 10 is amended to more distinctly claim the subject matter. Basis for the amendment is found throughout the specification (e.g., see page 45, lines 24-25). Claims 11 and 15 are amended to more distinctly claim the subject matter. Basis for the amendment is found throughout the specification (e.g., see page 45, lines 17-29). Claim 17 is amended to more distinctly claim the subject matter. Basis for the amendment is found throughout the specification (e.g., see original claim 42). Claim 35 is amended to more distinctly claim the subject matter. Basis for the amendment is found throughout the specification (e.g., see pages 31-40). No new matter is added.

CITATION OF REFERENCES

The Office Action states that the Information Disclosure Statement, filed October 5, 2004, was considered "to the extent it was possible to weed through the extensive listing of patents and publications irrelevant to the invention as instantly claimed" and invites the Applicant to identify and point out documents of particular relevance."

It is Applicant's understanding that, in accordance with MPEP Section 2001.04, patent applicants are advised to "submit information for consideration by the Office in applications rather than making and relying on their own determinations of materiality." This is precisely what Applicant has done.

The Relevant Law

The term "information" as used in 37 CFR §1.56 includes all of the kinds of information required to be disclosed and includes any information which is "material to patentability." In addition to prior art such as patents and publications, "information" under 37 CFR §1.56 includes, for example, information on possible prior public uses, sales, offers to sell, derived knowledge, prior invention by another and inventorship conflicts. See, *e.g.*, MPEP § 2001.04:

> "Materiality is not limited to prior art but embraces *any* information that a reasonable examiner would be substantially likely to consider important in deciding whether to allow an application to issue as a patent." *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1234, 66 USPQ2d 1481, 1486 (Fed. Cir. 2003) (emphasis in original).

Materiality is defined in 37 CFR 1.56(b) and discussed at MPEP §§ 2001.04-2001.05. Under the rule, information is not material unless it comes within the definition of 37 CFR 1.56(b)(1) or (2), which recites:

> (b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and
> (1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or
> (2) It refutes, or is inconsistent with, a position the applicant takes in:
> (i) Opposing an argument of unpatentability relied on by the Office, or
> (ii) Asserting an argument of patentability.

Information is "material" when there is a substantial likelihood that a reasonable examiner would have considered the information important in deciding whether to allow the application to issue as a patent. See *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1179, 33 USPQ2d 1823, 1827 (Fed. Cir. 1995).

Submission of Information Disclosure Statements in the instant application

Applicant takes exception with any suggestion of noncompliance with the duty of disclosure. Applicant has diligently endeavored to comply with the duty to disclose information material to patentability as set forth under 37 C.F.R. §1.56 and interpreted by the U.S. Patent and Trademark Office in Section 2001.04 of the Manual of Patent Examining Procedures.

The term "information" as used in 37 CFR §1.56 includes all of the kinds of information required to be disclosed and includes any information which is "material to patentability." In addition to prior art such as patents and publications, "information" under 37 CFR §1.56 includes, for example, information on possible prior public uses, sales, offers to sell, derived knowledge, prior invention by another and inventorship conflicts. MPEP § 2001.04 states that

> "Materiality is not limited to prior art but embraces *any* information that a reasonable examiner would be substantially likely to consider important in deciding whether to allow an application to issue as a patent." *Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1234, 66 USPQ2d 1481, 1486 (Fed. Cir. 2003) (emphasis in original).

Materiality is defined in 37 CFR 1.56(b) and discussed at MPEP §§ 2001.04-2001.05. Under the rule, information is not material unless it comes within the definition of 37 CFR 1.56(b)(1) or (2). Applicant notes that MPEP § 2001.04 states that:

> The definition of materiality in 37 CFR § 1.56 does not impose substantial new burdens on applicants, but is intended to provide the Office with the information it needs to make a proper and independent determination on patentability. **It is the patent examiner who should make the determination** after considering all the facts involved in the particular case. [emphasis added]

Applicant also directs the Examiner's attention to MPEP § 2001.05, which states:

> Under the rule, information is not material unless it comes within the definition of 37 CFR 1.56(b)(1) or (2). If information is not material, there is no duty to disclose the information to the Office. Thus, it is theoretically possible for applicants to draft claims and a specification to avoid a prima facie case of obviousness over a reference and then to be able to withhold the reference from the examiner. The Office believes that most applicants will wish to submit the information, however, even though they may not be required to do so, to strengthen the patent and avoid the risks of an incorrect judgment on their part on materiality or that it may be held that there was an intent to deceive the Office.

Applicant and Applicant's representative strongly object to any suggestion that either party has buried pertinent prior art or is in any way in violation of the duty of candor. In fully disclosing references as provided with the Information Disclosure Statement submitted on October 5, 2004, it was not, and is not, the intention of either party to bury prior art references or information. On the contrary, Applicant and Applicant's representative have endeavored to be in complete compliance with the duty of disclosure as set forth in the Patent Rules, and in accordance with the guidelines provided in the Manual of Patent Examining Procedure, by providing the Office with all references for consideration rather than making and relying on their own determinations of materiality.

As dictated by the Patent Rules in 37 CFR §1.97(h), the filing of an information disclosure statement shall not be considered to be an admission that the information cited in the statement is, or is considered to be, material to patentability as defined in 37 CFR §1.56. Furthermore, Applicant is unaware of any requirement in complying with the duty of disclosure to particularly point out references that are definitely pertinent to the claimed invention, especially in view of the revision of the former rule that required applicants to provide a statement of the relevance of information listed in an information disclosure statement.

Applicant and the undersigned take their duty of candor very seriously and in no way have attempted to bury or otherwise hide prior art or information from the Office. In the

instant application, Applicant has submitted in information disclosure statements and on PTO-1449 forms references that may be relevant to the patentability of the instant claims. Applicant met its duty of disclosure to the Office when it provided relevant references for the Examiner's consideration. See, *Molins PLC, supra*. The mere fact of submission of a large number of references has not been found to constitute an attempt to bury (*Molins PLC*, 48 F.3d at 1184).

Comments on Duty of Disclosure Issues

Finally, Office rules and procedures require that the Examiner not comment upon duty of disclosure issues. See, *e.g.*, MPEP 2010:

> ...the Office does not investigate and reject original or reissue applications under 37 CFR 1.56. Likewise, the Office ***will not comment*** upon duty of disclosure issues. . . such issues are ***no longer considered*** by the Office during its examination of patent applications. (emphasis added)

Therefore, notwithstanding the fact that Applicant has not breached its duty of disclosure, as discussed above, it is respectfully submitted that the comments made in the Office Action are inappropriate and should be withdrawn.

THE REJECTION OF CLAIMS 1-5, 6-12, 15-24, 26-44, 47 AND 49-64 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-5, 6-12, 15-24, 26-44, 47 and 49-64 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one of skill in the art to make and/or use the claimed subject matter. The Examiner states that the prior are would suggest that an ability to prolong a pregnancy at risk for preterm delivery is not a property known or common to the laundry list of progestational agents disclosed by Applicant, citing Goldstein *et al.* and Keirse in support of the allegation. The Examiner alleges that absent further guidance from the Applicant, random experimentation that is undue is required, and "one would not be assured of the ability to practice the invention commensurate in scope with these claims." Applicant respectfully traverses the rejection.

RELEVANT LAW

The test of enablement is whether one skilled in the art can make and use what is claimed based upon the disclosure in the application and information known to those of skill in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). A certain amount of experimentation is permissible as long as it is not undue. A patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent, Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987). Indeed, "not

everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted." *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332. Showing every combination of substituents is unnecessary.

A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *See, Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons experienced in the field of the invention. See *Vivid Technologies, Inc. v. American Science and Engineering, Inc.*, 200 F.3d 795, 804, 53 USPQ2d 1289, 1295 (Fed. Cir. 1999) ("patents are written by and for skilled artisans"). To hold otherwise would require every patent document to include a technical treatise for the unskilled reader. Although an accommodation to the "common experience" of lay persons may be feasible, it is an unnecessary burden for inventors and has long been rejected as a requirement of patent disclosures. See *Atmel Corp.*, 198 F.3d at 1382, 53 USPQ2d at 1230 (Fed. Cir. 1999) ("The specification would be of enormous and unnecessary length if one had to literally reinvent and describe the wheel."); *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983) ("Patents are written to enable those skilled in the art to practice the invention, not the public.")

THE CLAIMS

Claim 1 recites a combination that includes a test for detecting the presence of a fetal-restricted antigen or estriol in a sample and a progesterone-related agent or an omega-3 fatty acid. Claims 1-15 ultimately depend from claim 1 and are directed to various embodiments thereof.

Claim 17 recites a method of screening and treating a subject, where the method includes monitoring the level of a marker of preterm or imminent delivery in a body fluid sample from a subject following about 20 weeks of gestation; and if the level is indicative of a risk for preterm or imminent delivery, administering a progestational agent selected from among a naturally or synthetically produced omega-3 fatty acid, a naturally or synthetically produced hormone normally secreted by the corpus luteum, placenta, or adrenal cortex, and

derivatives and mixtures thereof, whereby delivery is delayed. Claims 18-25 and 27-34 ultimately depend from claim 17 and are directed to various embodiments thereof.

Claim 35 recites a method of screening and treating a subject, where the method includes detecting a fetal restricted antigen in a sample from a subject and assessing whether the level of fetal restricted antigen is indicative of a risk of preterm or imminent delivery. If the level of fetal restricted antigen is indicative of the risk, estriol is detected in a sample from a subject and the level of estriol is assessed to determine whether the level is indicative of a risk of preterm or imminent delivery. If the level of estriol is indicative of the risk, the level of a marker for membrane rupture is assessed and if the level of the marker for membrane rupture is not indicative of membrane rupture, a therapeutically effective amount of a progestational agent is administered to the subject, whereby delivery is delayed. Claims 36-64 ultimately depend from claim 35 and are directed to various embodiments thereof.

ANALYSIS

Factors for Consideration in Assessing the Amount of Experimentation

Consideration of the *In re Wands* factors with respect to the instant facts demonstrates that undue experimentation is not required to practice the claimed methods of screening and treating a subject at risk for preterm or imminent delivery.

a. Nature of the Invention

The specification provides a description of methods of screening and treating a subject at risk for preterm or imminent delivery. The instant claims are directed to methods of screening and treating a subject at risk for preterm or imminent delivery, one step of which is administering a progestational agent to delay delivery. The general principles of using progestational agents to delay delivery were well studied and developed at the time of filing of the instant application. In fact, the art indicates that studies in the 1970s were directed to testing the efficacy of progestational agents to inhibit preterm labor (*e.g.*, see Johnson *et al.*, N Engl J Med 293(14):675-680 (1975). Johnson *et al.* teaches that investigators as early as 1960 and 1963 advocated the use of progestational agents to inhibit premature labor (*Id.*, page 675, col. 1, second paragraph). The age of the art in this field is a strong factor supporting the view that the skilled artisan would have been familiar generally with progestational agents and their use. Therefore, the amount of disclosure required to meet the enablement requirement is minimal relative to other, less developed fields of study.

b. The Breadth of the Claims.

It is first noted that the claims are not directed to progestational agents or even to a method of administering a progestational agent. Rather, the claims are directed to therapeutic methods involving screening and treating subjects at risk for preterm or imminent delivery, one step of which is administering a progestational agent. The progestational agent is thus a component, many examples of which are known in the art, that is used in the claimed methods.

Second, as set forth in the claims, the progestational agent is any agent that favors, or is conducive to, gestation. Progestational agents, as described in the specification, include any of a group of hormones normally secreted by the corpus luteum and placenta, and in small amounts by the adrenal cortex, whether naturally or synthetically produced, and derivatives thereof.

Third, the instant application provides, and the art describes, many examples of such agents (see, for example, see Spicer *et al.*, U.S. Pat. No. 5,211,952 (1993), which is referred to in the instant application (page 11, lines 1-26), and teaches that progestational agents include dydrogesterone, ethynodiol diacetate, hydroxyprogesterone caproate, medroxyprogesterone acetate, norethindrone, norethindrone acetate, norethynodrel, norgestrel, progesterone, and megestrol acetate. The instant specification teaches progestational agents include gestagens, progestagens, progestins, progestogens, and progestational hormones. Further, the specification provides exemplary progestational agents, including dydrogesterone; ethynodiol diacetate; hydroxyprogesterone caproate; medroxyprogesterone acetate; norethindrone; norethindrone acetate; norethynodrel; norgestrel; megesterol acetate; gestodene; desogestrel; cingestol; lynestrenol; quingestanol acetate; levonorgestrel; 3-ketodesogestrel; norgestimate; osaterone; cyproterone acetate; trimegestone; dienogest; drospirenone; nomegestrol; (17-deacetyl)-norgestimnate; 19-norprogesterone; melengestrol; ethisterone; medroxyprogesterone acetate; 17α-hydroxyprogesterone; dimethisterone; ethinylestrenol; demegestone; promegestone; chlormadinone; pregn-4-ene-3,20-dione (progesterone); 19-nor-pregn-4-ene-3,20-dione; 17-hydroxy-19-nor-17α-pregn-5(10)-ene-20-yn-3-one; dl-11α-ethyl-17-ethinyl-17-α-hydroxygon-4-ene-3-one; 17-ethynyl-17-hydroxy-5(10)-estren-3-one; 17α-ethynyl-19-norestosterone; 6-chloro-17-hydroxypregna-4,6-diene-3,20-dione; 17α-hydroxy-6α-methyl-17(-1-propynl-)androst-4-ene-3-one; 9α,10α-pregna-4,6-diene-3,20-dione; 17-hydroxy-17α-pregn-4-en-20-yne-3-one; 19-nor-17α-preg-4-en-20-yen-3,17-diol; 17-hydroxy-pregn-4-ene-3,20-dione; 1-7-hydroxy-6α-methylpregn-4-ene-3,20-dione; and derivatives and mixtures

thereof, and naturally or synthetically produced omega-3 fatty acids, such as docosahexaenoic acid (DHA), and derivatives thereof.

The instant specification (*e.g.*, see page 11, line 1) teaches that a characteristic of progestational agents is that it inhibits or delays delivery. The specification teaches methods of administering the progestational agent, *e.g.*, orally, parenterally by injection (*e.g.*, by bolus injection or continuous infusion), transdermally, intranasally, or by inhalation (*e.g.*, see page 44, lines 6-9). The specification also teaches that optimal dosages for a given set of conditions can be ascertained using conventional dosage-determination tests and that administration of the progestational agent can be repeated at appropriate intervals (*e.g.*, see page 44, lines 10-19).

In light of the high level of skill in the art, the extensive teachings regarding progestational agents in the art, and the teachings of the specification, which provides exemplars of progestational agents, it is respectfully submitted that it would not require undue experimentation for a skilled artisan to select and use a progestational agent in the claimed methods. Accordingly, the breadth of the claims in referring to a progestational agent administered in a step of the claimed methods is commensurate with the description provided in the application.

c. Level of Skill in the Art

The level of skill in the art is high, as evidenced by the art in this area, which is authored primarily by those with Ph.D. and M.D. degrees. The art is intended for an audience of similarly highly skilled individuals, primarily in the fields of biochemical, pharmaceutical, or medical arts. The numerous articles and patents made of record in this application, authored and reviewed by those known in the art, address a highly skilled audience, and further evidence the high level of skill in this art.

d. State of the Art

At the time of the effective filing date of the claims, a broad body of knowledge had amassed in the areas of pharmaceutical sciences, medicine, and biochemistry directed to use of progestational agents. Keirse (Brit J Obstet Gynecology 97: 149-154) states that administration of progestational agents reduces the occurrence of preterm birth. Many progestational agents were known to those skilled in this art at the time the application was originally filed, including dydrogesterone, ethynodiol diacetate, hydroxyprogesterone caproate, medroxyprogesterone acetate, norethindrone, norethindrone acetate, norethynodrel, norgestrel, progesterone, and megestrol acetate (Spicer *et al.*, U.S. Pat. No. 5,211,952 (1993); 17α-hydroxyprogesterone caproate (Keirse, Brit J Obstet Gynecology 97: 149-154); acetoxypregnenolone, anagestone

acetate, chlormadinone acetate, desogestrol, dimethisterone, ethisterone, ethynodiol diacetate, fluorogestone acetate, gestodene, hydroxymethylprogesterone and derivatives thereof (*e.g.*, hydroxymethylprogesterone acetate), hydroxyprogesterone and derivatives thereof (*e.g.*, hydroxyprogesterone acetate and hydroxy- progesterone caproate), levonorgestrel, lynestenol, melengestrol acetate, norethindrone, norethindrone acetate, norgesterol, normethisterone, pregnenolone, and progesterone (Peters *et al.*, U.S. Pat. No. 5,321,044); 19-nor-pregn-4-ene-3,20-dione, 17-hydroxy-19-nor-17-α-pregn-5(10)-ene-20-yn-3-one, 17α-ethynyl-17-hydroxy-5(10)-estren-3-one, and 9β,10α-pregna-4,6-diene-3,20-dione (Theeuwes *et al.*, U.S. Pat. No. 4,014,334 (1977).

Thus, the prior art includes references that describe identifying, producing and/or extracting progestational agents, and using such compounds to reduce the occurrence of preterm birth. These references demonstrate the large volume of information regarding tested and reliable progestational agents and procedures for their use and administration available at the time of the effective filing date of the claims, and thus evidence the state of the art at the relevant time.

e. Predictability of the Art

It is alleged in the Office Action that there is still unpredictability in the art concerning the use of progestational agents because there are differences between the agents, including differences in teratogenic, metabolic or hemodynamic effects of natural progesterone compared to artificial progestagens. To support this assertion, the Office Action refers to Keirse and Goldstein *et al.* Applicant respectfully disagrees. Keirse teaches that Daya and Goldstein *et al.* reported separate meta-analyses assessing the effects of progesterone administration in pregnancy but reached contradictory conclusions. Keirse teaches that he conducted a third more-restricted meta-analysis using data from all placebo-controlled trials and concluded that administration of 17α-hydroxyprogesterone caproate does reduce the occurrence of preterm birth (Keirse, Brit J Obstet Gynecology 97, at page 149). Keirse teaches that of the various possible effects of progestagens considered by Goldstein *et al.*, the progestagens demonstrated a beneficial effect of premature birth, and that the study of Keirse indicated that injections of 17α-hydroxyprogesterone caproate may reduce the occurrence of preterm birth ((Keirse, Brit J Obstet Gynecology 97, at page 153). Keirse teaches that the evidence presented in the cited reference does not uphold the opinions of Goldstein *et al.* that no benefits have been demonstrated using progesterone treatment in pregnancy (page 153, col. 2, second full

paragraph). It is respectfully submitted that a report of an unsuccessful therapeutic association between progestational agents and miscarriage does not establish unpredictability of use of progestational agents to reduce the occurrence of preterm birth. There is no requirement that a therapeutic method be 100% effective in all indications to be considered predictable. As noted in the Keirse article, the effectiveness of progestational agents to reduce the occurrence of birth contrasts markedly with the poor effectiveness of other efforts to reduce the occurrence or preterm birth (Keirse, Brit J Obstet Gynecology 97, at page 154).

f. The Amount of Direction or Guidance Presented

The instant specification teaches each step of the claimed methods. The description provided in the instant application, combined with the extensive knowledge in the art of progestational agents that can be used in the steps of the methods, enable one of skill in the art to practice the claimed methods without undue experimentation. As set forth in the application, the detailed description of the steps of the claimed methods applies to all of the progestational agents provided therein.

In describing the step of administering a progestational agent to a subject, the instant specification provides teachings of what a progestational agent is, the desired qualities of a progestational agent and how it can physically be administered. The application further provides numerous examples of progestational agents that can be used in the claimed methods. Thus, for example, at page 10, lines 24-25 of the application, a progestational agent is described as a compound that favors, or is conducive to, gestation. The specification also describes techniques for, doses of agent for, and timing of administration of an agent to a subject (see, *e.g.*, pages 44-45, describing local and systemic administration, examples of blood levels of agent for use in determining doses and example doses).

g. The presence or absence of working examples

The specification teaches a number of examples. For example, the specification teaches that when the progestational agent is 17-α-hydroxyprogesterone caproate, an exemplary embodiment is administering the agent intramuscularly weekly at a dose of at least about 100 mg/week, to about at least 1000 mg/week, or the agent can be administered daily at a dose of at least about 10 mg/day to at least about 200 mg/day (*e.g.*, see page 44, lines 20-28). The specification teaches that another example of administering a progestational agent is selecting docosahexaenoic acid as the progestational agent, administering the agent orally either weekly at a dose of at least about 100 mg/week to about 2000 mg/week, or administering daily at a dose of at least about 10 mg/day to about 300 mg/day (*e.g.*, see page 44, line 29

through page 45, line 6). As set forth in the above analysis of the several factors to be considered in assessing the amount of experimentation required, when the relevant factors are applied to the instant facts and considered as a whole, it is clear that it would not require undue experimentation for a person skilled in the art to use the claimed methods.

h. The amount of experimentation required

There is nothing of record to suggest that the use of any of the claimed methods would require development of new procedures or excessive experimentation. Progestational agents useful in reducing preterm delivery are known in the art, as discussed above. Thus, any experimentation necessary to use the claimed methods is routine. "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. '***The key word is undue, not experimentation.***' " *In re Wands*, 858 F.2d at 737-38 (quoting *In re Angstadt*, 537 F.2d at 504; emphasis added; additional internal citations omitted). The art related to progestational agents, including that discussed above, demonstrates that such experimentation is not undue.

CONCLUSION

In light of the scope of the claims, the nature of the claimed subject matter, the state of the prior art, the high level of skill of those in this art, the predictability of the art, the direction and guidance presented in the specification, the low amount of experimentation required and the fact that any required experimentation is routine, Applicant respectfully submits that it would not require undue experimentation for a person skilled in the art to use the claimed methods. Therefore, the specification is enabling for using the full scope of the claimed subject matter. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

REJECTION OF CLAIMS 1-7, 10, 11, 15 AND 17-64 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-7, 10, 11, 15 and 17-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention. The Examiner alleges that the metes and bounds of the subject matter of claims 1-7 is unclear because no components are recited for the kit. Claims 10, 11 and 15 are rejected because the Examiner allege that it is unclear whether the additional antibodies are specific for the same or a different antigen. Claims 17-25 and 30-34

are rejected because it is alleged that elements preceded by the recitation "the" lack antecedent basis. Applicant respectfully traverses the bases for the rejections in turn below.

RELEVANT LAW

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. *Rosemount Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), *Caterpillar Tractor Co. v. Berco, S.P.A.*, 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof Glass Corp. v. Libby-Owens Ford Col.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

The failure to provide explicit antecedent basis for terms does not always render a claim indefinite. If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite. *Ex parte Porter*, 25 USPQ2d 1144, 1145 (Bd. Pat. App. & Inter. 1992) ("controlled stream of fluid" provided reasonable antecedent basis for "the controlled fluid"). Inherent components of elements recited have antecedent basis in the recitation of the components themselves. For example, the limitation "the outer surface of said sphere" would not require an antecedent recitation that the sphere has an outer surface.

CLAIMS

See related section above.

ANALYSIS

1. Claims 1-7

Claims 1-7 are rejected as allegedly indefinite because the metes and bounds encompassed by the claims allegedly is not clear because no components are recited for the kit. The Examiner also alleges that there is no antecedent basis for the recitation "the presence" in claim 1. Applicant respectfully submits that claim 1 as amended herein recites that the combination includes a test for detecting a fetal-restricted antigen or estriol in a sample; and a progesterone-related agent or an omega-3 fatty acid. Thus, the rejection is obviated.

2. Claim 4

Claim 4 is rejected because the Examiner alleges that the claim provides no further limitation on the combination because it only limits the intended use. Applicant respectfully disagrees. Claim 4 recites that the sample is a body fluid or a swab of the posterior fornix,

the cervical canal, the ectocervix and/or the external cervical os. The limitation further specifies the nature of the sample. Thus, it does not only limit an intended use.

3. Claims 10, 11 and 15

Claims 10, 11 and 15 are rejected because it is alleged that it is not clear if the additional antibodies are specific for the same antigen or a different antigen. Claim 10 specifies that the combination of claim 8, which includes an anti-(preterm delivery marker) antibody, further includes a second anti-(fetal restricted antigen) antibody directed to the same antigen. Claim 11 specifies that the combination of claim 8 further includes one or more anti-(membrane rupture marker) antibodies. Claim 15 specifies that the combination of claim 8, includes three or more antibodies, wherein the antibodies include an anti-fibronectin antibody, an anti-estriol antibody, and an anti-(insulin-like growth factor binding protein one) antibody. Applicant respectfully submits that as amended, the skilled artisan can determine the metes and bounds of claims 10, 11 and 15. Thus, the rejection of claims 10, 11 and 15 is obviated.

4. Claim 49

Claim 49 is rejected because the recitation "the therapeutically effective amount" allegedly lacks antecedent basis. Applicant respectfully submits that, as amended herein, claim 35, from which claim 49 depends, recites "the therapeutically effective amount." Thus, claim 35 provides antecedent basis for the recitation in claim 49. Therefore, the rejection as applied to claim 49 is obviated.

5. Claims 17-64

Claims 17-64 are rejected because the elements preceded by the word "the" allegedly lack antecedent basis. Applicant respectfully disagrees. Attention is directed to MPEP §2173.05(e) Lack of Antecedent Basis, which recites:

> A claim is indefinite when it contains words or phrases whose meaning is unclear. The lack of clarity could arise where a claim refers to "said lever" or "the lever," where the claim contains no earlier recitation or limitation of a lever and where it would be unclear as to what element the limitation was making reference. Similarly, if two different levers are recited earlier in the claim, the recitation of "said lever" in the same or subsequent claim would be unclear where it is uncertain which of the two levers was intended. A claim which refers to "said aluminum lever," but recites only "a lever" earlier in the claim, is indefinite because it is uncertain as to the lever to which reference is made. Obviously, however, the failure to provide explicit antecedent basis for terms does not always render a claim indefinite. If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite. *Ex parte Porter*, 25 USPQ2d 1144, 1145 (Bd. Pat. App. & Inter.

> 1992) ("controlled stream of fluid" provided reasonable antecedent basis for "the controlled fluid"). Inherent components of elements recited have antecedent basis in the recitation of the components themselves. For example, the limitation "the outer surface of said sphere" would not require an antecedent recitation that the sphere has an outer surface. See *Bose Corp. v. JBL, Inc.*, 274 F.3d 1354, 1359, 61 USPQ2d 1216, 1218-1219 (Fed. Cir. 2001) (holding that recitation of "an ellipse" provided antecedent basis for "an ellipse having a major diameter" because "[t]here can be no dispute that mathematically an inherent characteristic of an ellipse is a major diameter."

In this instance, the scope of the instant claims would be reasonably ascertainable by those skilled in the art.

a. "The" level of a marker

Claims 17-64 are rejected as indefinite because the recitation "*the* level of a marker" allegedly lacks antecedent basis. Applicant respectfully disagrees. As used in the claims, "the level" refers to a relative concentration of a marker. At any given point in time, there would be one concentration or level of a marker. Thus, the scope of the claim would be reasonably ascertainable by one skilled in the art. Hence, the claim is not indefinite.

b. "The" corpus luteum, placenta or adrenal cortex

Claim 17 is rejected as indefinite because the recitation "the corpus luteum, placenta or adrenal cortex" allegedly lacks antecedent basis. Applicant respectfully disagrees. Claim 17 recites that the progestational agent is selected from, *inter alia*, a naturally or synthetically produced hormone normally secreted by the corpus luteum, placenta or adrenal cortex." The corpus luteum is a glandular mass in the ovary that secretes a progesterone (*e.g.*, see Dorland's Illustrated Medical Dictionary, 27th ed. (1988), page 384). The placenta is a mammalian organ that during pregnancy joins mother to offspring, provides endocrine secretion and selective exchange of soluble blood-borne substances (*e.g.*, see Dorland's Illustrated Medical Dictionary, 27th ed. (1988), page 1300). The adrenal cortex is the outer layer of the adrenal gland that secretes steroid hormones, including mineralocorticoids, glucocorticoids, androgens and progestins (*e.g.*, see Dorland's Illustrated Medical Dictionary, 27th ed. (1988), page 386). Because a subject has one corpus luteum, one placenta and adrenal cortex, reference to "the corpus luteum," "the placenta" or "the adrenal cortex" is appropriate. Antecedent basis for the recitations "the corpus luteum," "the placenta" or "the adrenal cortex" is the recitation "a subject" because these are components of a subject. Thus, the scope of the claim would be reasonably ascertainable by those skilled in the art. Hence, the claim is not indefinite.

c. "The" ratio

Claim 21 is rejected as indefinite because the recitation "the ratio" in the phrase "the marker is the ratio of estriol to progesterone" lacks antecedent basis. Applicant respectfully disagrees. The specification teaches that the level of estriol and the level of progesterone are measured and that the ratio of estriol to progesterone is used as an indicator of preterm or imminent delivery. A ratio is the relationship between two quantities, usually expressed as the quotient of two numbers. The quotient of any two numbers results in a single result – the ratio. Accordingly, it is appropriate to refer to the quotient of any two numbers as the ratio. Thus, the scope of the claim would be reasonably ascertainable by those skilled in the art. Hence, the claim is not indefinite.

d. "The" posterior fornix, "the" cervical canal, "the" ectocervix and/or "the" external cervical os

Claims 4, 36, 53 and 54 are rejected as indefinite because they allegedly lack antecedent basis for the recitations "*the* posterior fornix," "*the* cervical canal," "*the* ectocervix" and/or "*the* external cervical os." Applicant respectfully disagrees. The claims reference. A female subject has one cervical canal, which is a canal in the cervix of the uterus that extends from the internal os to the external os (*e.g., see* Taber's Cyclopedic Medical Dictionary, 14th ed. (1981), page 227). The protrusion of the cervix uteri (cavity of the uterus) into the vagina forms the anterior and posterior fornix uteri ((*e.g., see* Taber's Cyclopedic Medical Dictionary, 14th ed. (1981), page 556). The ectocervix is the part of the uterine cervix lined with startified squamous epithelium (*e.g.*, Dorland's Illustrated Medical Dictionary, 27th ed. (1988), page 528). Thus, a female subject has one posterior fornix, one cervical canal, one ectocervix and one external cervical os. Antecedent basis for the recitations "the posterior fornix," "the cervical canal," "the ectocervix" and/or "the external cervical os" is the recitation "a subject" because these are components of a subject. Accordingly, because the sample is from a subject, and a female subject only has has one posterior fornix, one cervical canal, one ectocervix and one external cervical os, the scope of the claim would be reasonably ascertainable by those skilled in the art. Hence, the claim is not indefinite.

e. "The" start of fetal organogenesis

Claim 39 is rejected as indefinite because the recitation "*the* start of fetal organogenesis" allegedly lacks antecedent basis. Applicant respectfully disagrees. The "start" of fetal organogenesis refers to a point in time. There is one "start" of fetal

organogenesis. The recitation conveys to one of skill in the art that the progestational agent is administered after fetal organogenesis commences. Thus, the scope of a claim would be reasonably ascertainable by those skilled in the art. Hence, the claim is not indefinite.

REJECTION OF CLAIM 16 UNDER 35 U.S.C. §102(b)

Claim 16 is rejected under 35 U.S.C. § 102(b) as anticipated by Meis *et al.* (Am J Obstet Gynecol 187: S54 (2002)) or Johnson *et al.* (NEJM 293: 675 (1975)) or Yemini *et al.* (Am J Obstet Gynecol 151: 574 (1985)) or Noblot *et al.* (Eur J Obstet Gynecol Rep Biol 40: 203 (1991)) because each of these references alone allegedly discloses methods essentially as claimed.

Without addressing the propriety of the rejection, in order to advance prosecution of the application to allowance, claim 16 is cancelled herein without prejudice or disclaimer. Thus, the rejections under 35 U.S.C. § 102(b) are moot.

THE REJECTION OF CLAIMS 1-13, 15-19, 22-26, 30, 31, 33-44 AND 47-64 UNDER 35 U.S.C. §103(a)

Claims 1-13, 15-19, 22-26, 30, 31, 33-44 and 47-64 are rejected under 35 U.S.C. §103(a) over Leavitt *et al.* (WO 94/17405) in view of any of Johnson *et al.* (NEJM 293: 675, 1975), Meis *et al.*, (Am J Obstet Gynecol 187: S54, 2002) or Keirse (Br J Obstet Gynecol 97: 149, 1990) and further in view of Weiner *et al.* or Andersen *et al.* Leavitt *et al.* allegedly teaches every element of the claims except the use of estriol determination as a biochemical marker of impending preterm labor and the use of progestational agents as the agents to prolong pregnancy determined to be at risk for preterm delivery in the absence of ruptured membranes, but the teachings of Johnson *et al.* or Meis *et al.*, or Keirse in combination with Weiner *et al.* or Andersen *et al.* allegedly cures this deficiency. The Examiner alleges that any of Johnson *et al.*, Meis *et al.* or Keirse teaches the efficacy of progesterone treatments in reducing preterm delivery and that Weiner *et al.* or Andersen *et al.* teaches that treatment with tocolytic agents is not beneficial in patients with membrane rupture. The Examiner alleges that one of ordinary skill in the art would have tested a pregnant patient determined to have biochemical markers indicative of impending preterm delivery for the status of the fetal membranes and to treat those patients with intact fetal membranes indicated as at risk for having impending delivery with a pregnancy-prolonging agent because of the direct suggestion in Leavitt *et al.* to do so. The Examiner further alleges that it would have been obvious to treat a patient so identified with a known efficacious pregnancy-prolonging agent

such as progesterone in light of the teachings of any of Johnson *et al.*, Meis *et al.* or Keirse. Applicant respectfully traverses the rejection.

RELEVANT LAW

Under 35 U.S.C. §103, in order to set forth a case of *prima facie* obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. *See, e.g., Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *see, also, In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963).

Further, that which is within the capabilities of one of ordinary skill in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.*, 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

THE CLAIMS

See related section above.

TEACHINGS OF THE CITED ART

Leavitt *et al.* (WO 94/17405)

Leavitt *et al.* teaches assays that distinguish between subjects with impending immediate delivery with intact membranes from those in whom the membranes have ruptured. The method includes obtaining a cervicovaginal secretion sample from a pregnant patient determined to be at risk for imminent delivery by detection of a biochemical marker for

imminent delivery in a cervicovaginal secretion sample from the patient and determining the level of IGFBP-1 in the sample. If the level of IGFBP-1 is elevated, the patient has rupture of membranes, and if IGFBP-1 is not present, the patient has intact membranes (*e.g.*, see page 3, line 29 through page 4, line 4). Leavitt *et al.* teaches that a biochemical marker for imminent delivery includes fetal fibronectin and that the presence of an elevated fibronectin level in the sample indicates an increased risk of imminent delivery (*e.g.*, see page 4, lines 5-14).

Johnson *et al.* (NEJM 293: 675, 1975)

Johnson *et al.* teaches a possible obstetric use of 17α-hydroxyprogesterone caproate in the prevention of premature labor. Johnson *et al.* teaches that a double-blind study in 43 high-risk patients was done to determine the efficacy of 17α-hydroxyprogesterone caproate in preventing premature delivery (page 675, col. 1). Johnson *et al.* teaches that a decrease in maternal plasma progesterone is followed by the onset of labor and that a number of investigators advocate the clinical use of progestational agents to inhibit premature labor (page 675, col. 1, second paragraph). Johnson *et al.* teaches that 17α-hydroxyprogesterone caproate is a potent and long-acting progestagen (*Id.*). Johnson *et al.* teaches that large-scale trials are necessary to show the relevance of 17α-hydroxyprogesterone caproate to the prevention of prematurity in other populations at high risk (page 680, first paragraph). Johnson teaches factors to select patients who may be at high risk, but provides no suggestion for identifying patients who are at risk for preterm delivery.

Meis (Am J Obstet Gynecol 187: S54, 2002)

Meis teaches that small studies from the 1970s and 1980s suggested a benefit of 17α-hydroxyprogesterone therapy in preventing preterm birth, and a larger double-blind study was undertaken. Meis teaches that treatment with 17α-hydroxyprogesterone significantly reduced the risk of preterm birth in women at high risk. Meis, as Johnson *et al.*, relies on patient histories to identify subjects for administration of 17α-hydroxyprogesterone,

Keirse (Br J Obstet Gynecol 97: 149, 1990)

Keirse teaches a meta-analysis of controlled trials of a variety of progestational agents and concludes that there is no support that 17α-hydroxyprogesterone caproate protects against miscarriage but suggests that it does reduce the occurrence of preterm birth. Keirse teaches that 17α-hydroxyprogesterone caproate is the most fully studied progestational agent (page 149, col. 2, last full paragraph). Keirse teaches that its study indicates that injections of 17α-hydroxyprogesterone caproate may reduce the occurrence of preterm birth among women so

treated (page 153, col. 2, second full paragraph). Keirse did not provide the criteria for identifying women at risk of preterm delivery.

Weiner *et al.* (Am J Obstet Gynecol 159: 216-222 (1988))

Weiner *et al.* teaches preterm premature rupture of the membranes is associated with 40% of preterm deliveries (page 216, col. 1, first paragraph). Hence, Weiner *et al.* teaches that bed rest is generally accepted as the preferred management for the uninfected patient with preterm premature rupture of the membranes who is not in labor (*Id.*). Weiner *et al.* teaches that many physicians refrain from the use of tocolytic agents in women with preterm premature rupture of the membranes because tocolytic agent efficacy and safety in this subgroup are not clear (*Id.*). Weiner *et al.* teaches that the tocolytic agents used in their facility include ritodrine, terbutaline and magnesium sulfate (page 218, col. 1, lines 5-7). Weiner *et al.* teaches that tocolysis for preterm labor preceded by rupture of membranes are directed to delaying delivery only to administer corticosteroids in the hope of accelerating fetal lung maturity (*Id.*). Weiner *et al.* teaches that the use of tocolysis for preterm labor associated with intact membranes improves neonatal outcome (page 221, col. 1, first paragraph). Weiner *et al.* teaches that there is a paucity of information concerning either the efficacy or safety of tocolysis for labor after preterm premature rupture of the membranes (page 221, col. 1, last paragraph). Weiner *et al.* teaches that treatment of labor after preterm premature rupture of the membranes does not improve perinatal outcome after 28 weeks gestation (page 222, first paragraph).

Weiner *et al.* is virtually of no relevance to any of the instant claims. The instant claims are directed to methods and products for screening and treating women at risk of preterm delivery with progestational agents. Weiner *et al.* is concerned with women with ruptured membranes and the use of tocolytic agents, not progestational agents, for treatment of such subjects.

Andersen *et al.*

Andersen *et al.* teaches that preterm labor is a major problem in obstetrics, and that about a third of preterm births are associated with preterm premature rupture of membranes (PROM) (page 336, col. 1, second full paragraph). Andersen *et al.* teaches that in some instances preterm labor follows PROM, while in other situations preterm delivery becomes medically indicated because of the development of infection or other pregnancy complications (*Id.*). Andersen *et al.* suggests that progesterone withdrawal plays an important role in the onset of labor, finding lower progesterone levels in patients in preterm labor than in normal

controls but that prostaglandins play a more important role in the onset of labor (page 337, col. 2, second and third paragraphs). Andersen *et al.* teaches that progesterone injections have been suggested to prevent preterm delivery but are ineffective at stopping established preterm labor (page 345, col. 2, fourth paragraph). Andersen *et al.* teaches that weekly injections of 17α-hydroxyprogesterone caproate is used in prophylactic therapy in women at high risk for preterm delivery (*Id.*). Andersen *et al.* teaches that the diagnosis of preterm PROM is made by a sterile speculum examination with pooling fluid in the vaginal vault, positive Nitrazine tests and ferning of a dried smear of the fluid (page 346, col. 1, third paragraph). Andersen *et al.* that preterm labor should be treated promptly with tocolytic drugs if amnionitis or infection is not present, because once labor is more actively established treatment is less likely to be efficacious (page 349, col. 1, first full paragraph). Hence Anderson *et al.* is of little relevance to the instant claims, since it is directed to the use of tocolytic therapy and factors to consider in assessing the risk of preterm labor following premature rupture of membranes (PROM)

ANALYSIS

It is respectfully submitted that the Examiner has failed to set forth a case of prima facie obviousness for the following reasons.

The combination of the teachings of Leavitt *et al.* and Johnson *et al.* or Meis or Keirse with the teachings of Weiner *et al.* or Andersen *et al.* does not result in the instantly claimed methods.

1. Claim 1

Claim 1 and dependent claims include as elements a test system for detecting the presence of a fetal-restricted antigen or estriol in a sample, wherein the detected fetal-restricted antigen or estriol is indicative of a risk of preterm delivery; and a progesterone-related agent or an omega-3 fatty acid.

Leavitt *et al.* does not teach or suggest a combination that includes a test system for detecting a fetal-restricted antigen or estriol in a sample, and a progesterone-related agent or an omega-3 fatty acid. Leavitt *et al.* teaches assays that distinguish between subjects with impending immediate delivery with intact membranes from those in whom the membranes have ruptured. Leavitt *et al.* does not teach or suggest a test system for detecting estriol in a sample or a progesterone-related agent or an omega-3 fatty acid. Leavitt *et al.* does not teach or suggest administering a progestational agent.

Johnson *et al.* does not cure these deficiencies. Johnson *et al.* identifies its patients as at high risk if they had two spontaneous abortions immediately before the current pregnancy

of one premature delivery and one spontaneous abortion immediately preceding the present pregnancy, or two or more premature deliveries (page 675, col. 2, first full paragraph). Johnson *et al.* teaches use of 17α-hydroxyprogesterone caproate in the prevention of premature labor in patients categorized as high-risk. Johnson *et al.* provides no suggestion for testing subjects to identify those at risk for preterm delivery by detecting a fetal-restricted antigen or estriol. Thus, the of Johnson *et al.* does not teach or suggest a test system for detecting a fetal-restricted antigen or estriol in a sample.

Meis does not cure these deficiencies. Meis teaches use of 17α-hydroxyprogesterone caproate in the prevention of premature labor in women with a documented history of a previous spontaneous preterm birth. Meis provides no motivation to combine a test for detecting a fetal-restricted antigen and a progesterone-related agent. Meis identifies its patients as at high risk if they have a documented history of a previous spontaneous preterm birth less than 37 weeks' gestational age. Meis does not suggest any modifications of its methods nor the detection of a fetal-restricted antigen or estriol in a sample.

Keirse does not cure these deficiencies. Keirse teaches that 17α-hydroxyprogesterone caproate reduces the occurrence of preterm birth in women considered to be at high risk of preterm delivery. Keirse does not suggest combining a test for detecting a fetal-restricted antigen and a progesterone-related agent. Keirse performed a meta-analysis or previously reported trials involving women *considered* to be at high risk for miscarriage or preterm delivery. Keirse does not teach or suggest testing the subjects to determine whether they were at risk for imminent or preterm delivery. Thus, the method of Keirse for selecting patients is complete onto itself and does not require the detection of a fetal-restricted antigen or estriol in a sample.

Appliant respectfully submits that neither Weiner *et al.* nor Andersen *et al.* teaches or suggests the missing elements of the combination of the teachings of Leavitt *et al.* with the teachings of any of Johnson *et al* or Meis or Keirse. None of these references teaches or suggests a testing women with a test system for detecting a fetal-restricted antigen or estriol in a sample nor administering a progestational agent to such women, and, hence none suggests the combination of the elements of a test system and progestational agent.

Weiner *et al.* describes the therapeutic efficacy and cost-effectiveness of aggressive tocolyis using ritodrine, terbutaline and magnesium sulfate as tocolytic agents for premature labor associated with premature rupture of the membranes. Weiner *et al.* does not teach or suggest a test for detecting a fetal-restricted antigen, a progesterone-related agent or an

omega-3 fatty acid. Weiner *et al.*, which is concerned with tocolytic therapy of women with ruptured membranes, is of little relvance to the instant claims.

Andersen *et al.* teaches that progesterone injections have been suggested to prevent preterm delivery in patients having risk factors including demographic, medical risks in predtaing and current pregnancy and behavioral and environmetal risks for preterm birth. Andersen *et al.* teaches that weekly injections of 17α-hydroxyprogesterone caproate is used in prophylactic therapy in women with such risk factors. Andersen *et al.* does not teach or suggest employing a test for detecting a fetal-restricted antigen, a progesterone-related agent or an omega-3 fatty acid.

Thus, combining the teachings of Leavitt *et al.* with the teachings of any of Johnson *et al* or Meis or Keirse and Weiner *et al.* or Andersen *et al.*, alone or in any combination, does not result in the instantly claimed combination. None, singly nor in any combination thereof, suggests a test system for detecting a fetal-restricted antigen or estriol in a sample and a progestational agent. Claims 2-15 ultimately depend from claim 1 and include evey limitation thereof. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness of claims 1-15.

2. Claim 17

Claim 17 is directed to a method of screening and treating a subject, comprising by monitoring the level of a marker of preterm or imminent delivery in a body fluid sample from subject following about 20 weeks of gestation; and (b) if the level is indicative of a risk for preterm or imminent delivery, administering a progestational agent, whereby delivery is delayed.

Leavitt *et al.* does not teach or suggest a method of screening and treating a subject that includes as elements monitoring the level of a marker of preterm or imminent delivery in a body fluid sample from a subject following about 20 weeks of gestation, and if the level of the marker is indicative of a risk for preterm or imminent delivery, administering a progestational agent selected from among a naturally or synthetically produced omega-3 fatty acid, a naturally or synthetically produced hormone normally secreted by the corpus luteum, placenta, or adrenal cortex, and derivatives and mixtures thereof.

Leavitt *et al.* teaches assays that distinguish between subjects with impending immediate delivery with intact membranes from those in whom the membranes have ruptured. The method taught by Leavitt *et al.* includes determining the level of a biochemical marker for imminent delivery and determining the level of IGFBP-1 in the sample. Leavitt *et*

al. teaches that if the level of IGFBP-1 is elevated, the patient has rupture of membranes, and if IGFBP-1 is not present, the patient has intact membranes. Leavitt *et al.* does not teach or suggest use of progestational agents to prolong the pregnancy determined at risk for preterm delivery. Applicant respectfully submits that none of Johnson *et al.*, Meis nor Keirse teaches or suggests all of the elements missing from Leavitt *et al.*

Johnson *et al.* does not cure these deficiencies. Johnson *et al.* teaches use of 17α-hydroxyprogesterone caproate in the prevention of premature labor in patients categorized as high-risk. Johnson *et al.* identifies its patients as at high risk if they had two spontaneous abortions immediately before the current pregnancy of one premature delivery and one spontaneous abortion immediately preceding the present pregnancy, or two or more premature deliveries (page 675, col. 2, first full paragraph). Johnson *et al.* teaches administration of 17α-hydroxyprogesterone caproate at 16 weeks to any woman that meets certain criteria, and not to a population determined to be at risk. Hence, Johnson *et al.* teaches administering a progestational agent to a different population of women from the method of the instant claims and or at a different time period in the pregnancy. The population identified b Johnson *et al.* is not those who exhibit markers for preterm delivery in the existing pregnancy, but who previously had a preterm delivery. There is no consideration of the pregnancy at issue.

Meis teaches use of 17α-hydroxyprogesterone caproate in the prevention of premature labor in women with a documented history of a previous spontaneous preterm birth. Thus, Meis teaches administration of 17α-hydroxyprogesterone caproate to any woman who meets certain criteria, and not to a subject specifically determined to be at risk. Meis teaches that weekly injections of 17α-hydroxyprogesterone were initiated between 16 to 20 weeks gestation. Hence, Meis teaches administering a progestational agent to a different women and for or at a different period.

Keirse teaches that 17α-hydroxyprogesterone caproate reduces the occurrence of preterm birth in women considered to be at high risk of preterm delivery. Keirse does not teach or suggest testing the subjects to determine whether they were at risk for imminent or preterm delivery. Kierse teaches that in patients having a high preterm score, treatment started at 28-32 weeks and ended after 8 doses. Hence, Meis teaches administering a progestational agent to a different population of women and at a different period. Thus, combining the teachings of Leavitt *et al.* with the teachings of any of Johnson *et al* or Meis or

Keirse does not teach or suggest every element of the claimed method. Appliant respectfully submits that neither Weiner *et al.* nor Andersen *et al.* teaches or suggests the missing elements of the combination of the teachings of Leavitt *et al.* with the teachings of any of Johnson *et al* or Meis or Keirse.

Weiner *et al.* describes the therapeutic efficacy and cost-effectiveness of aggressive tocolyis using ritodrine, terbutaline and magnesium sulfate as tocolytic agents for premature labor associated with premature rupture of the membranes. Weiner *et al.* does not teach or suggest administering a progesterone-related agent or an omega-3 fatty acid. As noted, Weiner is of little or no relevance to any of the instant claims.

Andersen *et al.* teaches that progesterone injections have been suggested to prevent preterm delivery in patients having risk factors including demographic, medical risks in predtaing and current pregnancy and behavioral and environmetal risks for preterm birth. Andersen *et al.* does not teach or suggest a test for detecting a fetal-restricted antigen, a progesterone-related agent or an omega-3 fatty acid.

Thus, combining the teachings of Leavitt *et al.* with the teachings of any of Johnson *et al* or Meis or Keirse and Weiner *et al.* or Andersen *et al.*, alone or in any combination, does not result in the instantly claimed method. None, singly or in combination, teaches or suggests testing women after week 20 of the gestational period for particular markers and administering progestational therapy at the time a woman tests positive for a marker indicative of the risk. Claims 18-20 and 22-25 ultimately depend from claim 17 and include evey limitation thereof. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness of claims 17-20 and 22-25.

3. Claim 26

Leavitt *et al.* does not teach or suggest a method of screening and treating a subject that includes as elements monitoring the level of a first marker and a second marker of preterm or imminent delivery, and if the level of the first marker is indicative of a risk for preterm or imminent delivery, evaluating the level of the second marker, and if the level of the second marker is indicative of a risk for preterm delivery, administering a progestational agent, whereby delivery is delayed. Leavitt *et al.* teaches assays that distinguish between subjects with impending immediate delivery with intact membranes from those in whom the membranes have ruptured. The method taught by Leavitt *et al.* includes determining the level of a biochemical marker for imminent delivery and determining the level of IGFBP-1 in the sample. Leavitt *et al.* teaches that if the level of IGFBP-1 is elevated, the patient has rupture

of membranes, and if IGFBP-1 is not present, the patient has intact membranes. Leavitt *et al.* does not teach or suggest an assay that includes determining the level of a first marker and a second marker of preterm or imminent delivery. Leavitt *et al.* does not teach or suggest use of progestational agents to prolong the pregnancy determined at risk for preterm delivery. Applicant respectfully submits that none of Johnson *et al.*, Meis nor Keirse teaches or suggests all of the elements missing from Leavitt *et al.*

Johnson *et al.* teaches use of 17α-hydroxyprogesterone caproate in the prevention of premature labor in high-risk patients. Johnson *et al.* does not teach or suggest an assay that includes determining the level of a first marker and a second marker of preterm or imminent delivery.

Meis teaches use of 17α-hydroxyprogesterone caproate in the prevention of premature labor in women with a documented history of a previous spontaneous preterm birth. Meis does not teach or suggest an assay that includes determining the level of a first marker and a second marker of preterm or imminent delivery.

Keirse teaches that 17α-hydroxyprogesterone caproate reduces the occurrence of preterm birth. Keirse does not teach or suggest an assay that includes determining the level of a first marker and a second marker of preterm or imminent delivery. Thus, combining the teachings of Leavitt *et al.* with the teachings of any of Johnson *et al* or Meis or Keirse does not teach or suggest every element of the claimed method. Appliant respectfully submits that neither Weiner *et al.* nor Andersen *et al.* teaches or suggests the missing elements of the combination of the teachings of Leavitt *et al.* with the teachings of any of Johnson *et al* or Meis or Keirse.

Weiner *et al.* describes the therapeutic efficacy and cost-effectiveness of aggressive tocolyis for premature labor associated with premature rupture of the membranes. Weiner *et al.* teaches that treatment of labor after preterm premature rupture of the membranes does not improve perinatal outcome after 28 weeks gestation. Weiner *et al.* does not teach or suggest an assay that includes determining the level of a first marker and a second marker of preterm or imminent delivery.

Andersen *et al.* teaches that progesterone injections have been suggested to prevent preterm delivery but are ineffective at stopping established preterm labor. Andersen *et al.* teaches that weekly injections of 17α-hydroxyprogesterone caproate is used in prophylactic therapy in women at high risk for preterm delivery. Andersen *et al.* does not teach or suggest

an assay that includes determining the level of a first marker and a second marker of preterm or imminent delivery.

Thus, combining the teachings of Leavitt *et al.* with the teachings of any of Johnson *et al* or Meis or Keirse or Weiner *et al.* or Andersen *et al.*, alone or in any combination, does not result in the instantly claimed method of screening and treating a subject that includes monitoring the level of a first marker and a second marker of preterm or imminent delivery in a body fluid sample from a subject, where if the level of the first marker is indicative of a risk for preterm or imminent delivery, the level of the second marker is evaluated, and if the level of the second marker is indicative of a risk for preterm or imminent delivery, a progestational agent selected from among a naturally or synthetically produced omega-3 fatty acid, a naturally or synthetically produced hormone normally secreted by the corpus luteum, placenta, or adrenal cortex, and derivatives and mixtures thereof is administered, whereby delivery is delayed. Claims 27-34 ultimately depend from claim 26 and include evey limitation thereof. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness of claims 27-34.

4. Claim 35

Leavitt *et al.* does not teach or suggest a method of screening and treating a subject that includes as elements detecting a fetal restricted antigen in a sample from a subject and assessing whether the level of fetal restricted antigen is indicative of a risk of preterm or imminent delivery, and if the level of fetal restricted antigen is indicative of the risk, detecting estriol in a sample from a subject and assessing whether the level of estriol is indicative of a risk of preterm or imminent delivery, and if the level of estriol is indicative of the risk, assessing the level of a marker for membrane rupture and if the level of the marker for membrane rupture is not indicative of membrane rupture, administering a therapeutically effective amount of a progestational agent to the subject, whereby delivery is delayed. As discussed above, Leavitt *et al.* teaches assays that distinguish between subjects with impending immediate delivery with intact membranes from those in whom the membranes have ruptured. The method taught by Leavitt *et al.* includes determining the level of a biochemical marker for imminent delivery and determining the level of IGFBP-1 in the sample. Leavitt *et al.* does not teach or suggest an assay that includes determining the level of a fetal restricted antigen in a sample and if the level of the fetal restricted antigen is indicative of a risk or preterm or imminent delivery, detecting estriol in a sample. Leavitt *et al.* does not teach or suggest estriol as a biochemical marker for imminent delivery. Leavitt

et al. does not teach or suggest use of progestational agents to prolong the pregnancy determined at risk for preterm delivery. Applicant respectfully submits that none of Johnson *et al.*, Meis nor Keirse teaches or suggests the elements missing from Leavitt *et al.*

Johnson *et al.* teaches use of 17α-hydroxyprogesterone caproate in the prevention of premature labor in high-risk patients. Johnson *et al.* does not teach or suggest an assay that includes determining the level of a fetal restricted antigen in a sample and if the level of the fetal restricted antigen is indicative of a risk or preterm or imminent delivery, detecting estriol in a sample. Johnson *et al.* does not teach or suggest estriol as a biochemical marker for imminent delivery.

Meis teaches use of 17α-hydroxyprogesterone caproate in the prevention of premature labor in women with a documented history of a previous spontaneous preterm birth. Meis teaches that weekly injections of 17α-hydroxyprogesterone provided significant protection against recurrent preterm birth in women at high risk. Meis does not teach or suggest an assay that includes determining the level of a fetal restricted antigen in a sample and if the level of the fetal restricted antigen is indicative of a risk or preterm or imminent delivery, detecting estriol in a sample. Meis does not teach or suggest estriol as a biochemical marker for imminent delivery.

Keirse teaches that 17α-hydroxyprogesterone caproate reduces the occurrence of preterm birth. Keirse does not teach or suggest an assay that includes determining the level of a fetal restricted antigen in a sample and if the level of the fetal restricted antigen is indicative of a risk or preterm or imminent delivery, detecting estriol in a sample. Keirse does not teach or suggest estriol as a biochemical marker for imminent delivery. Thus, combining the teachings of Leavitt *et al.* with the teachings of any of Johnson *et al* or Meis or Keirse does not teach or suggest every element of the claimed method. Appliant respectfully submits that neither Weiner *et al.* nor Andersen *et al.* teaches or suggests the missing elements of the combination of the teachings of Leavitt *et al.* with the teachings of any of Johnson *et al* or Meis or Keirse.

Weiner *et al.* teaches that treatment of labor after preterm premature rupture of the membranes does not improve perinatal outcome after 28 weeks gestation. Weiner *et al.* does not teach or suggest an assay that includes determining the level of a fetal restricted antigen in a sample and if the level of the fetal restricted antigen is indicative of a risk or preterm or

imminent delivery, detecting estriol in a sample. Weiner *et al.* does not teach or suggest estriol as a biochemical marker for imminent delivery.

Andersen *et al.* teaches that progesterone injections have been suggested to prevent preterm delivery but are ineffective at stopping established preterm labor. Andersen *et al.* teaches that weekly injections of 17α-hydroxyprogesterone caproate is used in prophylactic therapy in women at high risk for preterm delivery. Andersen *et al.* does not teach or suggest an assay that includes determining the level of a fetal restricted antigen in a sample and if the level of the fetal restricted antigen is indicative of a risk or preterm or imminent delivery, detecting estriol in a sample. Andersen *et al.* does not teach or suggest estriol as a biochemical marker for imminent delivery.

Thus, combining the teachings of Leavitt *et al.* with the teachings of any of Johnson *et al* or Meis or Keirse or Weiner *et al.* or Andersen *et al.*, alone or in any combination, does not result in the instantly claimed method of screening and treating a subject that includes detecting a fetal restricted antigen in a sample from a subject and assessing whether the level of fetal restricted antigen is indicative of a risk of preterm or imminent delivery, and if the level of fetal restricted antigen is indicative of the risk, detecting estriol in a sample from a subject and assessing whether the level of estriol is indicative of a risk of preterm or imminent delivery, and if the level of estriol is indicative of the risk, assessing the level of a marker for membrane rupture, and if the level of the marker for membrane rupture is not indicative of membrane rupture, administering a therapeutically effective amount of a progestational agent to the subject, whereby delivery is delayed. Claims 36-64 ultimately depend from caim 35 and include every limitation thereof. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness of claims 35-64.

THE REJECTION OF CLAIMS 20, 21 AND 32 UNDER 35 U.S.C. §103(a)

Claims 20, 21 and 32 are rejected under 35 U.S.C. §103(a) over Leavitt *et al.* in view of any of Johnson *et al.*, Meis *et al.* or Keirse and further in view of Weiner *et al.* or Andersen *et al.* as applied to claims 1-13, 15-19, 22-26, 30, 31, 33-44 and 47-64 and further in view of Dullien (U.S. Pat. No. 5,480,776). The Examiner alleges that the combination of the teachings of Leavitt *et al.* in view of any of Johnson *et al.*, Meis *et al.* or Keirse and further in view of Weiner *et al.* or Andersen *et al.* teaches every element of claims 20, 21 and 32 except determining levels of unconjugated estriol as indicative of impending preterm labor, but alleges that Dullien cures this defect. Applicant respecftully traverses the rejection.

RELEVANT LAW

See related section above.

THE CLAIMS

See related section above. Claims 20 and 32 ultimately depend from claim 17.

TEACHINGS OF THE CITED ART

See related section above.

Dullien (U.S. Pat. No. 5,480,776)

Dullien teaches a method for detecting the onset of labor in a patient. The method includes analyzing a body fluid of the patient for estriol concentration, correlating the concentration with a standard value and relating a higher concentration of estriol relative to the standard value as an indication of potential onset of pre-term labor, where the method does not require determination of an estriol/progesterone concentration ratio in the body fluid being tested (col. 2, lines 19-33). Dullien teaches that the assay for estriol can be performed on any body fluid, and that saliva is preferred because unlike urine, detection is not complicated by the presence of estrogen conjugates (col. 2, lines 54-61).

ANALYSIS

As discussed above, combining the teachings of Leavitt *et al.* with the teachings of any of Johnson *et al* or Meis or Keirse and Weiner *et al.* or Andersen *et al.*, alone or in any combination, does not result in the instantly claimed method of claim 17. Claims 20, 21 and 32 ultimately depend from claim 17 and include evey limitation thereof. Applicant respctfully submits that Dullien does not teach or suggest the elements missing from the teachings of Leavitt *et al.* with the teachings of any of Johnson *et al* or Meis or Keirse and Weiner *et al.* or Andersen *et al.*

Dullien teaches a method for detecting the onset of labor in a patient that includes analyzing a body fluid of the patient for estriol concentration at from weeks 20-38. Dullien does not teach or suggest a method that includes administering a progestational agent selected from among a naturally or synthetically produced omega-3 fatty acid, a naturally or synthetically produced hormone normally secreted by the corpus luteum, placenta, or adrenal cortex, and derivatives and mixtures thereof. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness of claims 20, 21 and 32.

THE REJECTION OF CLAIMS 14, 45 AND 46 UNDER 35 U.S.C. §103(a)

Claims 14, 45 and 46 are rejected under 35 U.S.C. §103(a) over Leavitt *et al.* in view of any of Johnson *et al.*, Meis *et al.* or Keirse and further in view of Weiner *et al.* or Andersen *et al.* as applied to claims 1-13, 15-19, 22-26, 30-31, 33-44 and 47-64 and further in view of Allen *et al.* (Exp. Biol. Med. 226: 498 (2001)) or Olsen *et al.* (Lancet 339: 1003 (1992)). The Examiner alleges that the combination of the teachings of Leavitt *et al.* in view of any of Johnson *et al.*, Meis *et al.* or Keirse and further in view of Weiner *et al.* or Andersen *et al.* teaches every element of claims 14, 45 and 46 except omega-3 fatty acids as a pregnancy-prolonging agent, but the Examiner alleges that the teachings of either Allen *et al.* or Olsen *et al.* cures this deficiency. Applicant respectfully traverses the rejection.

RELEVANT LAW

See related section above.

THE CLAIMS

See related section above. Claim 14 ultimately depends from claim 1 and claims 45 and 46 ultimately depend from claim 35.

TEACHINGS OF THE CITED ART

See related section above.

Allen *et al.* (Exp. Biol. Med. 226: 498 (2001)

Allen *et al.* teaches that n-3 fatty acids may play a role in gestation and parturition. Allen *et al.* teaches that several human pregnancy supplementation trials with n-3 fatty acids have shown a significant reduction in the incidence of premature delivery and increased birth weight associated with increased gestational duration (page 498, col. 1). Allen *et al.* teaches that supplementation with long-chain n-3 fatty acids such as docosahexaenoic acid (DHA) may be useful in prolonging the duration of gestation in some high-risk pregnancy (*Id.*). Allen *et al.* teaches that a positive increase in gestational length was observed with dietary n-3 fatty acid supplementation (page 502, col. 1, second paragraph). Allen *et al.* teaches that the evidence linking n-3 fatty acid intakes and changes in maternal n-3 fatty acid status with alterations in gestational length is strong (page 503, col. 2, last paragraph).

Olsen *et al.* (Lancet 339: 1003 (1992)

Olsen *et al.* teaches that fish oil supplementation in the third trimester seems to prolong pregnancy without detrimental effects on the growth of the fetus or on the course of labor (page 1003, col. 1, last paragraph). Olsen *et al.* teaches that a diet rich in long-chain n-

3 fatty acids prolongs gestation, possibly by delaying initiation of labor and cervical ripening by inhibiting the production of prostaglandins and increasing the production of prostacyclins (page 1003, col. 2, last paragraph). Olsen *et al.* teaches that average gestation, birth weight and birth length was greatest in the fish-oil group and lowest in the olive oil group (page 1005, col. 2, first paragraph). Olsen *et al.* teaches that there is a dose-response relation up to a level of saturation between dietary fish oil and duration of gestation (page 1006, col2, first paragraph). Olsen *et al.* teaches that dietary marine n-3 fatty acids have a regulatory function in the process leading to the initiation of parturition in human beings, possibly by shifting the balance of the production of eicosanoids in favor of those derived from n-3 rather than n-6 fatty acids (page 1007, col. 1, first paragraph).

ANALYSIS

1. Claim 14

Claim 14 ultimately depends from claim 1. As discussed above, combining the teachings of Leavitt *et al.* with the teachings of any of Johnson *et al* or Meis or Keirse and Weiner *et al.* or Andersen *et al.*, alone or in any combination, does not result in the instantly claimed combination of claim 1. Applicant respectfully submits that neither Allen *et al.* nor Olsen *et al.* teaches or suggests the elements missing from the combination of Leavitt *et al.* with the teachings of Johnson *et al.* or Meis or Keirse and with the teachings of Weiner *et al.* or Andersen *et al.*

Allen *et al.* teaches that diet supplementation with long-chain n-3 fatty acids such as docosahexaenoic acid (DHA) may be useful in prolonging the duration of gestation in some high-risk pregnancy. Allen *et al.* does not teach or suggest a test for detecting a fetal-restricted antigen or estriol in a sample. Thus, combing the teachings of Leavitt *et al.* with the teachings of Johnson *et al.* or Meis or Keirse and with the teachings of Weiner *et al.* or Andersen *et al.* and the teachings of Allen *et al.* does not result in every element of claim 14.

Olsen *et al.* does not teach or suggest the elements missing from the combination of the teachings of Leavitt *et al.* with the teachings of Johnson *et al.* or Meis or Keirse and with the teachings of Weiner *et al.* or Andersen *et al.* Olsen *et al.* teaches that a diet rich in long-chain n-3 fatty acids prolongs gestation, possibly by delaying initiation of labor and cervical ripening by inhibiting the production of prostaglandins and increasing the production of prostacyclins. Olsen *et al.* does not teach or suggest a test for detecting a fetal-restricted antigen or estriol in a sample. Thus, combing the teachings of Leavitt *et al.* with the teachings of Johnson *et al.* or Meis or Keirse and with the teachings of Weiner *et al.* or

Andersen *et al.* and the teachings of Olsen *et al.* does not result in every element of claim 14. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness of claim 14.

2. Claims 45 and 46

Claims 45 and 46 ultimately depend from claim 35. As discussed above, combining the teachings of Leavitt *et al.* with the teachings of any of Johnson *et al* or Meis or Keirse and Weiner *et al.* or Andersen *et al.*, alone or in any combination, does not result in the instantly claimed combination of claim 35. Applicant respectfully submits that neither Allen *et al.* nor Olsen *et al.* teaches or suggests the elements missing from the combination of Leavitt *et al.* with the teachings of Johnson *et al.* or Meis or Keirse and with the teachings of Weiner *et al.* or Andersen *et al.*

Allen *et al.* teaches that diet supplementation with long-chain n-3 fatty acids such as docosahexaenoic acid (DHA) may be useful in prolonging the duration of gestation in some high-risk pregnancy. Allen *et al.* does not teach or suggest detecting estriol in a sample and if the estriol is indicative of a risk of preterm or immediate delivery, assessing the level of a marker for membrane rupture. Thus, combing the teachings of Leavitt *et al.* with the teachings of Johnson *et al.* or Meis or Keirse and with the teachings of Weiner *et al.* or Andersen *et al.* and the teachings of Allen *et al.* does not result in every element of claims 45 and 46.

Olsen *et al.* does not teach or suggest the elements missing from the combination of the teachings of Leavitt *et al.* with the teachings of Johnson *et al.* or Meis or Keirse and with the teachings of Weiner *et al.* or Andersen *et al.* Olsen *et al.* teaches that a diet rich in long-chain n-3 fatty acids prolongs gestation, possibly by delaying initiation of labor and cervical ripening by inhibiting the production of prostaglandins and increasing the production of prostacyclins. Olsen *et al.* does not teach or suggest detecting estriol in a sample and if the estriol is indicative of a risk of preterm or immediate delivery, assessing the level of a marker for membrane rupture. Thus, combing the teachings of Leavitt *et al.* with the teachings of Johnson *et al.* or Meis or Keirse and with the teachings of Weiner *et al.* or Andersen *et al.* and the teachings of Olsen *et al.* does not result in every element of claims 45 and 46. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness of claims 45 and 46.

Other Art

The Examiner cites a number of references that, although allegedly not relied upon as a basis for rejection of any claims, are considered pertinent to the Applicant's disclosure. The references cited by the Examiner include Yemini *et al.* (Am J Obstet Gynecol 151: 574,

1985), Noblot *et al.* (Eur J Obstet Gynecol Rep Biol 40:203, 1991), Dullien (US 5,370,135), Terao *et al.* (US 5,650,394), Lockwood *et al.* (NEJM 325(10): 669-674, 1991), Senyei *et al.* (US 5,468,619), Kanayama *et al.* (Acta Obstet Gynecol Scand 70: 29-34, 1991) and Rutanen *et al.* (Am J Obstet Gynecol 164(1): 258, Abstract No. 38, 1991), Rutanen (WO 92/12426), Rutanen *et al.* (Clinica Chimica Acta 214(1): 73, 1993) and Rutanen *et al.* (Clinica Chimica Acta 253: 91, 1996).

Because none of the art was cited in a rejection of the pending claims, Applicant makes no comment on the art considered by the Examiner to be pertinent to the Applicant's disclosure but not relied upon as a basis for rejection of any claims.

* * *

In view of the above, examination of the application on the merits and allowance is respectfully requested.

Respectfully submitted,

Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 17101-025001 / 826
Address all correspondence to:
Stephanie Seidman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 678-5070
Facsimile: (202) 626-7796
email: seidman@fr.com